

# Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk

**Philip Urban<sup>1,2\*</sup>, Roxana Mehran<sup>3</sup>, Roisin Collieran<sup>4</sup>,  
Dominick J. Angiolillo<sup>5</sup>, Robert A. Byrne<sup>4</sup>, Davide Capodanno<sup>6,7</sup>,  
Thomas Cuisset<sup>8</sup>, Donald Cutlip<sup>9</sup>, Pedro Eerdmans<sup>10</sup>, John Eikelboom<sup>11</sup>,  
Andrew Farb<sup>12</sup>, C. Michael Gibson<sup>13,14</sup>, John Gregson<sup>15</sup>, Michael Haude<sup>16</sup>,  
Stefan K. James<sup>17</sup>, Hyo-Soo Kim<sup>18</sup>, Takeshi Kimura<sup>19</sup>, Akihide Konishi<sup>20</sup>,  
John Laschinger<sup>12</sup>, Martin B. Leon<sup>21,22</sup>, P.F. Adrian Magee<sup>12</sup>, Yoshiaki Mitsutake<sup>20</sup>,  
Darren Mylotte<sup>23</sup>, Stuart Pocock<sup>15</sup>, Matthew J. Price<sup>24</sup>, Sunil V. Rao<sup>25</sup>,  
Ernest Spitzer<sup>26,27</sup>, Norman Stockbridge<sup>12</sup>, Marco Valgimigli<sup>28</sup>,  
Olivier Varenne<sup>29,30</sup>, Ute Windhoevel<sup>2</sup>, Robert W. Yeh<sup>31</sup>,  
Mitchell W. Krucoff<sup>25,32</sup>, Marie-Claude Morice<sup>2</sup>**

<sup>1</sup>La Tour Hospital, Geneva, Switzerland; <sup>2</sup>Cardiovascular European Research Center, Massy, France; <sup>3</sup>Icahn School of Medicine at Mount Sinai, New York, NY; <sup>4</sup>Deutsches Herzzentrum München, Technische Universität München, Germany; <sup>5</sup>Division of Cardiology, University of Florida College of Medicine, Jacksonville; <sup>6</sup>Cardio-Thoracic-Vascular Department, Centro Alte Specialità e Trapianti, Catania, Italy; <sup>7</sup>Azienda Ospedaliero Universitario "Vittorio Emanuele-Policlinico," University of Catania, Italy; <sup>8</sup>Département de Cardiologie, Centre Hospitalier Universitaire Timone and Inserm, Inra, Centre de recherche en cardiovasculaire et nutrition, Faculté de Médecine, Aix-Marseille Université, Marseille, France; <sup>9</sup>Cardiology Division, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; <sup>10</sup>Head of the Notified Body, DEKRA Certification B.V.; <sup>11</sup>Department of Medicine, McMaster University, Hamilton, Canada; <sup>12</sup>US Food and Drug Administration, Silver Spring, MD; <sup>13</sup>Harvard Medical School, Boston, MA; <sup>14</sup>Baim Institute for Clinical Research, Brookline, MA; <sup>15</sup>London School of Hygiene and Tropical Medicine, UK; <sup>16</sup>Städtische Kliniken Neuss, Lukaskrankenhaus GmbH, Germany; <sup>17</sup>Department of Medical Sciences and Uppsala Clinical Research Center, Uppsala University, Sweden; <sup>18</sup>Cardiovascular Center, Seoul National University Hospital, Korea; <sup>19</sup>Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Japan; <sup>20</sup>Office of Medical Devices 1, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan; <sup>21</sup>Columbia University Medical Center, New York, NY; <sup>22</sup>Cardiovascular Research Foundation, New York, NY; <sup>23</sup>University Hospital and National University of Ireland, Galway; <sup>24</sup>Scripps Clinic, La Jolla, CA; <sup>25</sup>Duke Clinical Research Institute, Durham, NC; <sup>26</sup>Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands; <sup>27</sup>Cardiology, Clinical Trial Management and Core Laboratories, Rotterdam, the Netherlands; <sup>28</sup>Department of Cardiology, Inselspital, University of Bern, Switzerland; <sup>29</sup>Service de Cardiologie, Hôpital Cochin, Assistance publique - hôpitaux de Paris, Paris, France; <sup>30</sup>Université Paris Descartes, Sorbonne Paris-Cité, France; <sup>31</sup>Beth Israel Deaconess Medical Center, Boston, MA; <sup>32</sup>Duke University Medical Center, Durham, NC

Identification and management of patients at high bleeding risk undergoing percutaneous coronary intervention are of major importance, but a lack of standardization in defining this population limits trial design, data interpretation, and clinical decision-making. The Academic Research Consortium for High Bleeding Risk (ARC-HBR) is a collaboration among leading research organizations, regulatory authorities, and physician-scientists from the United States, Asia, and Europe focusing on percutaneous coronary intervention-related bleeding. Two

\* Correspondence: Philip Urban, MD, Hôpital de la Tour, 1 Ave Maillard, 1217 Geneva, Switzerland. Email: [philip.urban@latour.ch](mailto:philip.urban@latour.ch)

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meetings of the 31-member consortium were held in Washington, DC, in April 2018 and in Paris, France, in October 2018. These meetings were organized by the Cardiovascular European Research Center on behalf of the ARC-HBR group and included representatives of the US Food and Drug Administration and the Japanese Pharmaceuticals and Medical Devices Agency, as well as observers from the pharmaceutical and medical device industries. A consensus definition of patients at high bleeding risk was developed that was based on review of the available evidence. The definition is intended to provide consistency in defining this population for clinical trials and to complement clinical decision-making and regulatory review. The proposed ARC-HBR consensus document represents the first pragmatic approach to a consistent definition of high bleeding risk in clinical trials evaluating the safety and effectiveness of devices and drug regimens for patients undergoing percutaneous coronary intervention.

## Keywords

clinical trial protocols as topic • hemorrhage • percutaneous coronary intervention

## Abbreviations

|       |                                       |
|-------|---------------------------------------|
| ACS   | acute coronary syndrome               |
| AF    | atrial fibrillation                   |
| ARC   | Academic Research Consortium          |
| BARC  | Bleeding Academic Research Consortium |
| bAVM  | brain arteriovenous malformation      |
| BMS   | bare metal stent                      |
| CAD   | coronary artery disease               |
| CKD   | chronic kidney disease                |
| DAPT  | dual antiplatelet therapy             |
| DES   | drug-eluting stent                    |
| eGFR  | estimated glomerular filtration rate  |
| HBR   | high bleeding risk                    |
| HR    | hazard ratio                          |
| ICH   | intracranial hemorrhage               |
| NIS   | Nationwide Inpatient Sample           |
| NSAID | nonsteroidal anti-inflammatory drug   |
| OAC   | oral anticoagulant                    |
| OR    | odds ratio                            |
| PCI   | percutaneous coronary intervention    |
| TIA   | transient ischemic attack             |
| VKA   | vitamin K antagonist                  |

The evolution of percutaneous coronary intervention (PCI) over the last 40 years has facilitated treatment of increasingly complex patient populations. One such population comprises patients at high bleeding risk (HBR). In early trials of first-generation drug-eluting stents (DES), the protocol-recommended dual antiplatelet therapy (DAPT) duration was 3 to 6 months, but as a result of concerns about late thrombotic events, this was increased to 12 months in studies initiated after 2006.<sup>1</sup> Coinciding with this shift, patients considered to be at HBR were either excluded from or underrepresented in clinical trials. The accepted practice in such patients was bare metal stent (BMS) implantation, given that 1 month of DAPT was considered sufficient at that time. Until recently, even more inclusive studies of contemporary DES continued to exclude patients for whom guideline-recommended DAPT was considered unsuitable.<sup>2,3</sup>

Recently, 3 randomized trials comparing DES and BMS with 1 month of DAPT in patients perceived to be at increased bleeding risk

showed superior safety and efficacy with DES.<sup>4–6</sup> These reports quickly generated global attention as an important public health concern given that, as recently as 2014, BMSs were used in 20% of coronary stenting procedures in patients  $\geq 65$  years of age in the United States, with 18.2% of BMS recipients having a predicted bleeding risk of  $\geq 5\%/y$ .<sup>7</sup>

The challenges in defining the optimal management of patients undergoing PCI at HBR include a paucity of relevant clinical data and the use of heterogeneous definitions of HBR that limit interpretation, generalization, and pooling of published data. In 2006, the first Academic Research Consortium (ARC) provided standardized definitions of ischemic end points for coronary stent trials, and in 2011, the Bleeding ARC (BARC) provided bleeding end point definitions, both of which have gained wide acceptance in clinical study design, demonstrating the value of consensus-based definitions in the PCI field.<sup>8,9</sup>

With this in mind, the aim of the ARC-HBR initiative is to define HBR in patients undergoing PCI on the basis of a literature review and clinical consensus with the primary goal of advancing the consistency and quality of data collection and reporting, thereby supporting organizations tasked with making recommendations for clinical practice or regulatory decisions.<sup>10</sup> To this end, 2 meetings of the ARC-HBR group were organized by the Cardiovascular European Research Center (Massy, France) in Washington, DC, in April 2018 and Paris, France, in October 2018. International academic experts; representatives of the US Food and Drug Administration, the Japanese Pharmaceuticals and Medical Devices Agency, and a European Notified Body (DEKRA, Arnhem, the Netherlands); and observers from the device and pharmaceutical industries attended (participants are listed in the Appendix in the online-only [Data Supplement](#)).

## Contemporary clinical trials of coronary stents and antiplatelet therapy: not generalizable to patients at HBR

Regulatory approval processes for medical devices differ between jurisdictions.<sup>11</sup> In the United States, for example, completed pivotal randomized trials of investigational DES submitted for US Food and

**Table 1** One-year bleeding rates in trials of antiplatelet therapy after coronary stenting

| Trial (Year of Publication)         | Patients, n | Type of Patients           | Inclusion of Periprocedural Bleeding | Overall Bleeding, % | Bleeding Definition Used | Adjudication of Bleeding Events |
|-------------------------------------|-------------|----------------------------|--------------------------------------|---------------------|--------------------------|---------------------------------|
| RESET (2012) <sup>25</sup>          | 2117        | Selected low bleeding risk | Yes                                  | 0.7                 | TIMI major or minor      | CEC adjudicated                 |
| EXCELLENT (2012) <sup>26</sup>      | 1443        | Selected low bleeding risk | Yes                                  | 1                   | TIMI major or minor      | CEC adjudicated                 |
| ARCTIC (2012) <sup>27</sup>         | 2440        | All comers                 | Yes                                  | 2.8                 | STEEPLE major            | CEC adjudicated                 |
| PRODIGY (2012) <sup>28</sup>        | 1970        | All comers                 | No (first 30 d excluded)             | 2.0†                | BARC 3 or 5              | CEC adjudicated                 |
| OPTIMIZE (2013) <sup>29</sup>       | 3119        | Selected low bleeding risk | Yes                                  | 0.5                 | Protocol-defined         | CEC adjudicated                 |
| DAPT* (2014) <sup>30</sup>          | 22 866      | Selected low bleeding risk | Yes                                  | 2.7                 | GUSTO moderate or severe | CEC adjudicated                 |
| SECURITY (2014) <sup>31</sup>       | 1399        | Selected low bleeding risk | Yes                                  | 0.9                 | BARC 3 or 5              | CEC adjudicated                 |
| PRECISE-DAPT (2017) <sup>32</sup>   | 14 963      | Selected low bleeding risk | No (first 7 d excluded)              | 1.5                 | TIMI major or minor      | CEC adjudicated                 |
| SMART-DATE (2018) <sup>34</sup>     | 2712        | ACS                        | Yes                                  | 0.3†                | BARC 3 or 5              | CEC adjudicated                 |
| GLOBAL LEADERS (2018) <sup>33</sup> | 15 968      | All comers                 | Yes                                  | 1.9†                | BARC 3 or 5              | Site reported                   |

Bleeding definitions are shown in the Appendix in the online-only [Data Supplement](#). ACS indicates acute coronary syndrome; ARCTIC, bedside monitoring to adjust antiplatelet therapy for coronary stenting; BARC, Bleeding Academic Research Consortium; CEC, Clinical Events Committee; DAPT, Dual Antiplatelet Therapy Trial; EXCELLENT, Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; GLOBAL LEADERS, Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment With the Endeavor; PRECISE-DAPT, Predicting Bleeding Complications In Patients Undergoing Stent Implantation and Subsequent Dual Anti Platelet Therapy; PRODIGY, Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study; RESET, Real Safety and Efficacy of 3-Month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation; SECURITY, Second Generation Drug-Eluting Stents Implantation Followed by Six Versus Twelve-Month Dual-Antiplatelet Therapy; SMART-DATE, Safety of 6-Month Duration of Dual Antiplatelet Therapy After Acute Coronary Syndromes; STEEPLE, Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation; and TIMI, Thrombolysis in Myocardial Infarction.

\*First year after enrollment, before randomization.

†One-year bleeding rates were obtained as personal communications from the principal investigators of these 3 trials.

Drug Administration review have been prospective, multicenter studies with high internal validity, but enrollment has been limited to highly selected patients and lesions.<sup>12–18</sup> Patients considered unsuitable for protocol-mandated DAPT duration have been excluded. Although more recent DES trials have had more liberal enrollment criteria, per protocol or de facto, they have continued to exclude patients with advanced renal impairment, prior bleeding, prior recent stroke, and hematologic abnormalities (Table 1 in the online-only [Data Supplement](#)).<sup>16–18</sup>

Many investigator-initiated “all-comer” randomized trials included some patients at increased bleeding risk.<sup>2,19–24</sup> However, only a minority of screened patients tend to be enrolled, mean patient age is similar to that in earlier trials, patients unsuitable for long-term DAPT continue to be systematically excluded, and details on the proportion of patients taking oral anticoagulation (OAC) or with other bleeding risk factors are not consistently reported.<sup>2,19–24</sup> Thus, despite broader inclusion criteria, subjects at HBR are still underrepresented in contemporary studies.

Clinical trials of DAPT strategies after stenting have also excluded patients at HBR, with reported major bleeding rates at 1 year varying between 0.3% and 2.8% (Table 1).<sup>25–34</sup>

## Contemporary clinical trials in patients at increased risk of bleeding

Three randomized trials investigating short DAPT durations have been completed in patients undergoing PCI perceived to be at increased bleeding risk,<sup>4–6</sup> and many trials are currently ongoing (Table II in the online-only [Data Supplement](#)). Inclusion criteria in these trials largely reflect exclusion criteria in prior DES studies of patients not at HBR receiving different DAPT durations, but there is significant heterogeneity with respect to the patient populations included.

Among completed studies, the LEADERS FREE trial (Polymer-free drug-coated coronary stents in patients at high bleeding risk; n=2466) was the trial most broadly inclusive of patients at HBR to date, with a mean of 1.7 bleeding risk criteria per patient.<sup>4</sup> The ZEUS trial (Zotarolimus-Eluting Endeavor Sprint Stent in Uncertain DES Candidates; n=1606) enrolled uncertain DES candidates on the basis of criteria for high thrombotic, restenotic, or bleeding risk,<sup>35</sup> with a prespecified subgroup analysis of patients who met criteria for HBR

(ZEUS-HBR;  $n=828$ ).<sup>5</sup> The SENIOR trial (Drug-eluting stents in elderly patients with coronary artery disease: a randomized single-blind trial;  $n=1200$ ) included elderly patients with no other specified inclusion criteria associated with increased bleeding risk.<sup>6</sup> The most frequently met criterion associated with increased bleeding risk in all 3 trials was advanced age (in 64%, 51%, and 100% of patients in LEADERS FREE, ZEUS-HBR, and SENIOR, respectively), although the lower cutoff for age differed between trials ( $>80$  years in ZEUS-HBR versus  $\geq 75$  years in LEADERS FREE and SENIOR). The second most frequently met characteristic was indication for OAC in 36%, 38%, and 18% of patients, respectively. Although renal impairment was the third most commonly met criterion in LEADERS FREE (19%), it was not a prespecified criterion for HBR status in ZEUS-HBR. Early planned surgery was a bleeding risk inclusion criterion in LEADERS FREE (met in 16% of patients), but such patients were excluded in ZEUS-HBR and SENIOR. Prior hemorrhagic stroke was also an inclusion criterion in LEADERS FREE but was an exclusion criterion in SENIOR, and although it was not an exclusion criterion in ZEUS-HBR, no information on its prevalence is provided. Bleeding rates according to inclusion criteria in LEADERS FREE are shown in Table III in the online-only [Data Supplement](#).

The differences in eligibility criteria and enrolled patient populations in completed trials are reflected in the differences in bleeding event rates. In LEADERS FREE and ZEUS-HBR, the 1-year rates of BARC 3 to 5 bleeding in patients treated with 1-month DAPT after PCI were 7.3% and 4.2%, respectively, and in the SENIOR trial, the 1-year BARC 3 to 5 bleeding rate in patients treated with 1 to 6 months of DAPT after PCI was  $\approx 3.5\%$ . Such differences highlight the need for a standardized definition of HBR.

## Currently available bleeding risk scores

At least 6 scores have been developed that predict long-term bleeding risk in patients taking antiplatelet therapy.<sup>32,36–39</sup> The 2017 European Society of Cardiology focused update on DAPT in coronary artery disease (CAD) recommended (Class IIb recommendation, Level of Evidence A) that the use of risk scores such as the PRECISE-DAPT (Predicting Bleeding Complications In Patients Undergoing Stent Implantation and Subsequent Dual Anti Platelet Therapy) and DAPT scores may be considered to guide antiplatelet therapy after PCI.<sup>40</sup>

The main features of existing scores are summarized in Table 2, and the variables in each score are shown in Table IV in the online-only [Data Supplement](#).<sup>32,36–39,41</sup> Advanced age is the only variable common to all scores, but age cutoffs for increased bleeding risk and their relative weights vary between risk scores. In addition, although baseline anemia was found to be one of the strongest independent predictors of bleeding assessed in PARIS (patterns of non-adherence to anti-platelet regimens in stented patients), BleedMACS (Bleeding Complications in an Multicenter Registry of Patients Discharged With Diagnosis of Acute Coronary Syndrome), the Dutch aspirin score, and PRECISE-DAPT,<sup>32,36–38</sup> it was not assessed in the development of the REACH (Reduction of Atherothrombosis for Continued Health Registry) or DAPT score.<sup>39,41</sup> Moreover, definitions of anemia differed between studies.

Five variables (prior malignancy, congestive heart failure, body mass index  $<25$  or  $\geq 35$   $\text{kg/m}^2$ , hypercholesterolemia, and elevated white cell count) are present in only 1 score. Furthermore, all scores omit certain important variables known to be associated with HBR because their prevalence is low in patients with CAD or those undergoing PCI (eg, severe liver disease, bleeding diatheses, or thrombocytopenia), because they were rarely recorded in the derivation data sets (eg, history of cancer or prior bleeding, use of nonsteroidal anti-inflammatory drugs [NSAIDs], or planned surgery), or because collinearity with other selected predictors may have overshadowed their significance.

Such differences in risk prediction scores reflect heterogeneity in the patient populations studied, the variables assessed (and their definitions), and the bleeding definitions used in the development cohorts. At best, these scores have moderate accuracy for predicting bleeding, with C statistics in the development cohorts ranging from 0.64 to 0.73 (Table 2). Moreover, none of these scores was validated in HBR patient populations, highlighting the need for standardized HBR criteria for evaluating such patients.

## Defining HBR criteria

HBR is defined as a BARC 3 or 5 bleeding risk of  $\geq 4\%$  at 1 year or a risk of an intracranial hemorrhage (ICH) of  $\geq 1\%$  at 1 year. Thus, a major criterion for ARC-HBR is defined as any criterion that, in isolation, is considered to confer a BARC 3 or 5 bleeding risk of  $\geq 4\%$  at 1 year or any criterion considered to be associated with a risk of ICH of  $\geq 1\%$  at 1 year. A minor criterion for ARC-HBR is defined as any criterion that, in isolation, is considered to confer increased bleeding risk, with a BARC 3 or 5 bleeding rate of  $<4\%$  at 1 year.

The cutoff value of 4% for BARC 3 or 5 bleeding was based on consensus of the participants, taking into account that 1-year major bleeding rates in trials of DAPT after PCI, which largely excluded patients at HBR, were  $<3\%$  (Table 1) and that, in DES trials enrolling patients at HBR, 1-year BARC 3 to 5 bleeding rates were higher (7.2% in LEADERS FREE [with 1.7 HBR criteria per patient] and 4.2% in ZEUS-HBR despite only 1 month of DAPT after PCI) and 3.5% in the SENIOR trial (in which age  $\geq 75$  years was the sole inclusion criterion).

## Proposed HBR definition

Twenty clinical criteria were identified as major or minor by consensus, supported by published evidence (Table 3 and Figure). Patients are considered to be at HBR if at least 1 major or 2 minor criteria are met. The definition is thus binary. Although it is recognized that the coexistence of increasing numbers of risk factors for bleeding is associated with a stepwise increase in risk of BARC 3 to 5 bleeding,<sup>5</sup> sufficient data are not currently available to create a point-based score that would take into account the relative weight of each HBR criterion. Nonetheless, the presence of increasing numbers of major or minor criteria in any patient further increases bleeding risk, which may be considered in clinical decision-making and clinical trial analysis. The proposed consensus-based definition takes into account the available evidence for patients at HBR undergoing PCI and is

**Table 2** Scores assessing long-term bleeding risk in patients taking antiplatelet therapy

|                                      | REACH39                   | Dutch ASA Score37                                | DAPT41*  | PARIS38                                     | PRECISE-DAPT32  | BleeMACS36                             |
|--------------------------------------|---------------------------|--|--|---|---|--|
| Year of publication                  | 2010                      | 2014   | 2016   | 2016  | 2017  | 2018                                   |
| Development data set                 | REACH registry            | Dutch ASA registry                               | DAPT randomized trial                          | PARIS registry                              | Pooled analysis of 8 randomized trials                  | BleeMACS registry                      |
| Development data set, n              | 56 616                    | 235 531  | 11 648   | 4190  | 14 963  | 15 401                                 |
| Patient population                   | Risk of atherothrombosis† | New low-dose aspirin users                       | Stable and event-free patients 12 mo after PCI | Stable and unstable patients undergoing PCI | Stable and unstable patients undergoing PCI             | Patients with ACS undergoing PCI       |
| Bleeding outcome                     | Serious bleeding at 2 y   | Upper GI bleeding at a median follow-up of 530 d | Major bleeding between 12 and 30 mo after PCI  | Major bleeding at 2 y                       | Out-of-hospital bleeding at a median follow-up of 552 d | Serious spontaneous bleeding at 1 y    |
| Bleeding definition used             | Protocol-defined          | First episode of upper GI bleeding               | GUSTO moderate or severe                       | BARC 3 or 5                                 | TIMI major or minor                                     | Protocol-defined                       |
| Proportion of patients at HBR        | 25% (score >11)           | 83.1% (score ≥1)                                 | 23.4% (score -2 to 0)                          | 8% (score ≥8)                               | 25% (score ≥25)   | 25% (score ≥26)                        |
| Rate of bleeding in the HBR subgroup | 2.76% (at 2 y)            | 1%–35% for scores from 2 to 13                   | 2.7% (between 13 and 30 mo)                    | 10.7% (at 2 y)                              | 1.8%–4.2% (at 1 y)                                      | 8.03% (at 1 y)                         |
| Also evaluates thrombotic risk       | No                        | No   | Yes  | Yes   | No  | No                                     |
| Score range                          | 0 to 23                   | 0 to 15  | -2 to 10                                       | 0 to 14                                     | 0 to 100  | 0 to 80                                |
| Development discrimination           | AUC 0.68                  | AUC 0.64   | AUC 0.68                                       | AUC 0.72                                    | AUC 0.73  | AUC 0.71 (0.72 in internal validation) |
| Validating data set                  | CHARISMA                  | Dutch health insurance database                  | PROTECT  | ADAPT-DES                                   | PLATO and Bern PCI registry                             | SWEDHEART                              |
| Validating dataset, n                | 15 603                    | 32 613   | 8136   | 8130  | 8595 and 6172   | 96 239                                 |
|                                      |                           |  |  |   |   | (ACS+PCI); 93,150 (ACS)                |
| Validation discrimination            | AUC 0.64                  | AUC 0.63   | AUC 0.64 (bleeding)                            | AUC 0.64                                    | AUC 0.70 and 0.66                                       | AUC 0.65                               |
|                                      |                           |  |  |   |   | (ACS+PCI); AUC 0.63 (ACS)              |

Bleeding definitions are shown in the Appendix in the online-only [Data Supplement](#). ACS indicates acute coronary syndrome; ADAPT-DES, Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents; ASA, aspirin; AUC, area under the curve; BARC, Bleeding Academic Research Consortium; BleeMACS, Bleeding Complications in a Multicenter Registry of Patients Discharged With Diagnosis of Acute Coronary Syndrome; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; DAPT, Dual Antiplatelet Therapy Trial; GI, gastrointestinal; GUSTO, Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries; HBR, high bleeding risk; PARIS, patterns of non-adherence to anti-platelet regimens in stented patients; PCI, percutaneous coronary intervention; PLATO, Platelet Inhibition and Patient Outcomes; PRECISE-DAPT, Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; PROTECT, Patient Related Outcomes With Endeavor Versus Cypher Stenting Trial; REACH, Reduction of Atherothrombosis for Continued Health Registry; and TIMI, Thrombolysis in Myocardial Infarction.

\*The DAPT score is not purely a bleeding risk score; rather, it is a score to predict benefit versus harm of prolonged dual antiplatelet therapy (>1 year) in patients after percutaneous coronary intervention. Thus, it integrates covariates independently associated with bleeding (but not ischemic) risk and vice versa.

†Risk of atherothrombosis in REACH was defined as cardiovascular disease, coronary artery disease, peripheral artery disease, or ≥3 cardiovascular risk factors.



**Table 3** Major and minor criteria for hbr at the time of PCI

| Major   | Minor   |
|---|---|
| Anticipated use of long-term oral anticoagulation*  | Age ≥75 y   |
| Severe or end-stage CKD (eGFR <30 mL/min)   | Moderate CKD (eGFR 30–59 mL/min)  |
| Hemoglobin <11 g/dL   | Hemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women  |
| Spontaneous bleeding requiring hospitalization or transfusion in the past 6 mo or at any time, if recurrent | Spontaneous bleeding requiring hospitalization or transfusion within the past 12 mo not meeting the major criterion |
| Moderate or severe baseline thrombocytopenia† (platelet count <100 × 10 <sup>9</sup> /L)                    | Long-term use of oral NSAIDs or steroids  |
| Chronic bleeding diathesis  | Any ischemic stroke at any time not meeting the major criterion   |
| Liver cirrhosis with portal hypertension  |   |
| Active malignancy‡ (excluding nonmelanoma skin cancer) within the past 12 mo                                |   |
| Previous spontaneous ICH (at any time)Previous traumatic ICH within the past 12 mo                          |   |
| Presence of a bAVM  |   |
| Moderate or severe ischemic stroke§ within the past 6 mo  |   |
| Nondeferrable major surgery on DAPT   |   |
| Recent major surgery or major trauma within 30 d before PCI   |   |

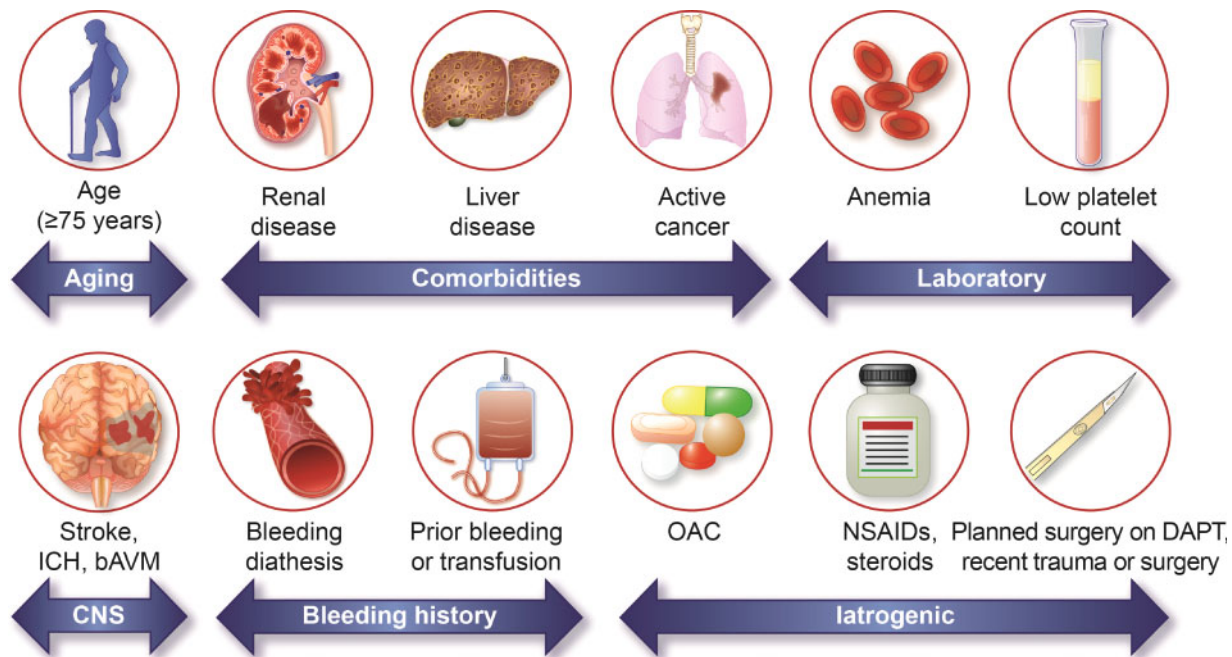
bAVM indicates brain arteriovenous malformation; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; HBR, high bleeding risk; ICH, intracranial hemorrhage; NSAID, nonsteroidal anti-inflammatory drug; and PCI, percutaneous coronary intervention.

\*This excludes vascular protection doses.<sup>42</sup>

†Baseline thrombocytopenia is defined as thrombocytopenia before PCI.

‡Active malignancy is defined as diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy).

§National Institutes of Health Stroke Scale score ≥5.



**Figure** Factors associated with an increased bleeding risk after percutaneous coronary intervention. bAVM indicates brain arteriovenous malformation; CNS, central nervous system; DAPT, dual antiplatelet treatment; ICH, intracranial hemorrhage; NSAID, nonsteroidal anti-inflammatory drug; and OAC, oral anticoagulation.

pragmatic for application to clinical trials supporting clinical practice recommendations and regulatory review. The criteria making up the definition are discussed below. Associated major (preferably BARC 3 or 5) bleeding rates or rates of ICH at 1 year are provided when available. Factors that were considered but not deemed HBR criteria are also discussed.

## Age

Age  $\geq 75$  years is considered a minor ARC-HBR criterion (Table 3).

Although elderly patients represent the fastest-growing patient subgroup undergoing PCI,<sup>43,44</sup> they tend to be underrepresented in randomized trials of DES and DAPT. In the SENIOR trial, which included patients  $\geq 75$  years of age (mean age,  $81.4 \pm 4.2$  years) treated with 1 or 6 months of DAPT after coronary stenting (DES versus BMS), the 1-year rate of BARC 3 to 5 bleeding was  $\approx 3.5\%$ . Indeed, elderly patients undergoing PCI tend to have more comorbidities and coexisting risk factors for bleeding compared with younger patients.<sup>45</sup> A substudy of elderly patients ( $\geq 75$  years) enrolled in the LEADERS FREE trial ( $n=1564$ ) showed that patients who qualified for inclusion on the basis of age alone ( $n=562$ ) had a lower rate of 1-year BARC 3 to 5 bleeding compared with the overall elderly population (3.2% versus 7.8%, respectively).<sup>46</sup> Nonetheless, in the development cohorts of bleeding risk scores in patients undergoing PCI, advanced age generally persisted as an independent predictor of bleeding after adjustment for coexisting bleeding risk factors.<sup>32,38,41,47–51</sup>

In a patient-level meta-analysis of 6 randomized trials ( $n=11\,473$ ) comparing short ( $\leq 6$  months) and longer (12 months) DAPT duration after PCI, short DAPT halved the rate of protocol-defined major bleeding at 1 year in patients  $\geq 65$  years of age (0.5% versus 1.1%; hazard ratio [HR], 0.46 [95% CI, 0.24–0.88];  $P=0.02$ ), without increasing ischemic events (2.4% versus 3.0%; HR, 0.84 [95% CI, 0.60–1.16];  $P=0.2856$ ). In contrast, in younger patients, short DAPT failed to reduce bleeding (0.3% versus 0.5%; HR, 0.59 [95% CI, 0.26–1.34];  $P=0.21$ ), but ischemic events were significantly increased (2.4% versus 1.4%; HR, 1.67 [95% CI, 1.14–2.44];  $P=0.0082$ ), suggesting differential bleeding–ischemic risk profiles in elderly versus younger patients after PCI.<sup>52</sup>

In summary, bleeding risk increases with age with some confounding resulting from comorbidities, which tend to accumulate in elderly patients. With this in mind, it must be acknowledged that biological age and chronological age may differ. Although the relationship between age and bleeding risk appears to be continuous, a pragmatic decision was made to use a binary variable in the current definition.

## Oral anticoagulation

The anticipated use of long-term OAC (with a vitamin K antagonist [VKA] or non-vitamin K OAC) after PCI is considered a major ARC-HBR criterion (Table 3).

The most common indication for OAC in patients undergoing PCI is coexisting atrial fibrillation (AF). When treating such patients, physicians must balance the risk of thromboembolism with AF, the risk of stent thrombosis and myocardial infarction after PCI, and the risk of bleeding on combined antithrombotic therapy.<sup>53</sup> Bleeding risk is magnified in the setting of triple antithrombotic therapy (OAC plus DAPT).<sup>54</sup>

In the WOEST trial (What Is the Optimal antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting;  $n=573$ ), 1-year rates of BARC 3 to 5 bleeding in patients on VKAs after PCI were 6.5% and 12.7% in the double (VKA plus clopidogrel) and triple (VKA plus aspirin and clopidogrel) therapy arms, respectively (HR, 0.49 [95% CI, 0.28–0.86];  $P=0.011$ ).<sup>55</sup> In the ISAR-TRIPLE trial (Intracoronary Stenting and Antithrombotic Regimen-Testing of a 6-Week versus a 6-Month Clopidogrel Treatment Regimen in Patients with Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting;  $n=614$ ), patients on a VKA undergoing PCI were randomized to treatment with triple therapy for 6 weeks versus 6 months, with continuation of VKA and aspirin thereafter.<sup>56</sup> At 9 months, rates of BARC 3 to 5 bleeding were  $\approx 11.1\%$  and  $10.4\%$ , respectively, with comparable bleeding event rates between treatment groups.

In the PIONEER AF-PCI trial (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) and RE-DUAL PCI trial (Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting), patients with AF undergoing PCI were allocated to treatment with dual therapy consisting of a non-vitamin K OAC and a P2Y<sub>12</sub> inhibitor or triple therapy consisting of a VKA, a P2Y<sub>12</sub> inhibitor, and aspirin. Although bleeding rates were lower in patients on dual therapy, it is unclear to what extent this was attributable to the omission of aspirin as opposed to the use of a non-vitamin K OAC instead of a VKA.<sup>57,58</sup> In PIONEER AF-PCI ( $n=2124$ ), 1-year BARC 3 to 5 bleeding rates were 4.1% with dual therapy including low-dose rivaroxaban (15 mg daily), 4.4% with triple therapy including very-low-dose rivaroxaban (2.5 mg twice daily), and 7.9% with triple therapy including a VKA. In RE-DUAL PCI ( $n=2725$ ), respective rates of TIMI (Thrombolysis in Myocardial Infarction) major/minor bleeding at 14 months were 3.0% versus 7.0% in patients treated with dual therapy with dabigatran 110 mg twice daily versus triple therapy with warfarin (HR, 0.41 [95% CI, 0.26–0.63];  $P<0.001$ ) and 3.5% versus 6.3% in those treated with dual therapy including dabigatran 150 mg twice daily versus triple therapy including warfarin (HR, 0.53 [95% CI, 0.33–0.85];  $P=0.009$ ). In both trials, bleeding rates in the groups treated with triple therapy with a VKA were markedly lower than those observed in WOEST and ISAR-TRIPLE, indicating an overall lower bleeding risk profile in the populations enrolled, possibly explained by the stricter patient selection criteria in PIONEER AF-PCI and RE-DUAL PCI.

Although bleeding risk may differ between VKAs and novel anticoagulants and between individual novel anticoagulants (Table V in the online-only Data Supplement) and different doses, exposure times and variations in renal function may confer differential bleeding risks. Weighting the relative bleeding risk with different OAC regimens is beyond the scope of this definition.

## Chronic kidney disease

Severe or end-stage chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR]  $<30$  mL/min) is considered a major ARC-HBR criterion, and moderate CKD (eGFR, 30–59 mL/min) is considered a minor ARC-HBR criterion (Table 3).

**Table 4** Impact of CKD on clinical outcomes after PCI

| CrCl, mL/min                    |                      | Major Bleeding                         |                | Ischemic Events  |  |                       |                  |
|---------------------------------|----------------------|--|----------------|------------------|--|-----------------------|------------------|
|                                 |                      | End Point(s) and Duration of Follow-Up | Event Rate, %  | P Value          | End Point(s) and Duration of Follow-Up           | Event Rate, %         | P Value          |
| EVENT registry62<br>(n=4791)    | >75 (n=2827, 59%)    | In-hospital TIMI major or              | 3.3/0.2        | <0.0001/0.56     | MI in hospital/at                                | 5.7/7.2               | <0.001/0.0007    |
|                                 | 50–75 (n=1253, 26%)  | minor bleeding, major                  | 5.0/0.3        |                  | 1 y  | 7.3/9.2               |                  |
|                                 | 30–49 (n=571, 12%)   | vascular complications,                | 8.8/1.2        |                  |  | 8.2/10.7              |                  |
|                                 | <30 (n=140, 3%)      | or transfusion/TIMI                    | 14.3/0.0       |                  |  | 10.0/11.4             |                  |
| ACUTY trial60<br>(n=13 819)     | ≥60 (n=11 350, 80.9) | major bleeding                         |                |                  |  |                       |                  |
|                                 | <60 (n=2469, 19.1%)  | ACUTY major bleeding at 30 d           | 3.6<br>9.2     | <0.0001          | Death resulting from any cause, MI, or un-       | 7.0/14.4<br>10.8/21.6 | <0.0001/0.001    |
| HORIZON-AMI trial61<br>(n=3397) | ≥60 (n=2843, 83.7%)  | ACUTY major bleeding                   | 5.7/6.0/6.7    | <0.0001/<0.0001/ | 1 y  | 4.3/10.1/19.8         | <0.0001/<0.0001/ |
|                                 | 30–60 (n=506, 14.9%) | at 30 d/1 y/2 y                        | 12.1/14.3/16.9 | <0.0001          | Death, reinfarction, TVR, or                     | 9.9/18.5/30.0         | <0.0001          |
|                                 | ≤30 (n=48, 1.4%)     |  | 45.2/45.2/45.2 |                  | stroke at 30 d/1 y/2 y                           | 29.2/49.3/70.0        |                  |
| PARIS Registry63<br>(n=4584)    | ≥60 (n=3745, 82.0%)  | BARC 3 or 5 bleeding at                | 3.04           | NR               | Cardiac death,                                   | 10.20                 | NR               |
|                                 | <60 (n=839, 18.0%)   | 2 y                                    | 8.94           |                  | probable/definite ST, or clinically indicated    | 16.81                 |                  |
| ADAPT-DES64<br>(n=8410)         | ≥60 (n=7043, 83.7%)  | ACUTY major bleeding                   | 7.5            | <0.001           | TVR at 2 y                                       | 9.9                   | <0.001           |
|                                 | <60 (n=1367 (16.3%)  | at 2 y                                 | 13.9           |                  | Cardiac death, MI, or ischemia-driven TLR at 2 y | 15.3                  |                  |

Bleeding definitions are shown in the Appendix in the online-only [Data Supplement](#). ACUTY indicates Acute Catheterization and Urgent Intervention Triage Strategy; ADAPT-DES, Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents; BARC, Bleeding Academic Research Consortium; CKD, chronic kidney disease; CrCl, creatinine clearance; EVENT, Evaluation of Drug Eluting Stents and Ischemic Events; HORIZON-AMI, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; MI, myocardial infarction; NR, not reported; PARIS, patterns of non-adherence to anti-platelet regimens in stented patients; PCI, percutaneous coronary intervention; ST, stent thrombosis; TIMI, Thrombolysis in Myocardial Infarction; TLR, target lesion revascularization; and TVR, target vessel revascularization.



Approximately 30% of patients undergoing PCI have an eGFR <60 mL/min,<sup>59</sup> but patients with severe CKD have generally been excluded from randomized trials. Even mild CKD is an independent risk factor for bleeding after PCI,<sup>60,61</sup> and the risk increases incrementally with worsening CKD (Table 4).<sup>60–64</sup> One mechanism may be reduced clearance of certain antithrombotic medications. In the PRECISE-DAPT bleeding risk score,<sup>32</sup> eGFR <30 mL/min in isolation places patients in the highest quartile for bleeding risk, whereas milder CKD is associated with a slightly to moderately increased bleeding risk.

The increased bleeding risk with CKD must be considered in the context of a proportionately increased risk of ischemic events (Table 4), making this balance more sensitive in patients with CKD compared with most other HBR criteria. In the DAPT score, a clinical decision tool to identify patients expected to derive benefit versus harm from prolonged DAPT after PCI, CKD is not a variable because the associated bleeding risk was balanced by an almost identical ischemic risk.<sup>41</sup>

From the data presented, the consensus decision was to use CKD stages rather than eGFR as a continuous variable in the definition (Table 4).

## Anemia

A hemoglobin level <11 g/dL is considered a major ARC-HBR criterion. A hemoglobin level of 11 to 12.9 g/dL for men and 11 to 11.9 g/dL for women is considered a minor ARC-HBR criterion (Table 3).

Anemia defined by World Health Organization criteria (hemoglobin <13 g/dL in men and <12 g/dL in women) is frequently encountered in patients undergoing PCI, with a reported prevalence of 21.6% in the Bern DES Registry.<sup>65</sup> Anemia correlates with the risk of future bleeding in patients undergoing PCI. The 1-year risk of BARC 3 or 5 bleeding in patients with acute coronary syndrome (ACS) treated with PCI followed by prasugrel or ticagrelor in the RENAMI registry (Registry of New Antiplatelets in Patients With Myocardial Infarction; n=4424) was significantly higher in patients with World Health Organization–defined anemia compared with those without (5.4% versus 1.5%, respectively;  $P=0.001$ ).<sup>66</sup> In a meta-analysis of 44 studies including >230 000 patients undergoing PCI, anemia (defined by World Health Organization criteria in the majority of studies) was present in 16% of patients and was associated with a 2-fold risk of subsequent bleeding (as defined in individual studies; adjusted risk ratio, 2.31 [95% CI, 1.44–3.71]), as well as an increased risk of ischemic events and mortality.<sup>67</sup> Furthermore, bleeding risk increased with increasing severity of anemia.

Baseline anemia was also found to be an important predictor of bleeding in the development cohorts of a number of bleeding risk scores. In PARIS, baseline anemia (hemoglobin <12 g/dL in men and <11 g/dL in women) was a strong predictor of 2-year BARC 3 or 5 bleeding (9.5% with versus 2.7% without anemia; adjusted HR, 2.72 [95% CI, 1.83–4.04];  $P<0.0001$ ).<sup>38</sup> In BleeMACS, hemoglobin <11 g/dL was the strongest predictor of serious spontaneous bleeding (defined in the Appendix in the online-only Data Supplement) at 1 year (adjusted HR, 2.41 [95% CI, 1.29–4.50];  $P<0.001$ ), and hemoglobin of 11.0 to 13.9 g/dL was also associated with a significantly increased bleeding risk (adjusted HR, 1.59 [95% CI, 1.14–2.21];  $P=0.006$ ) compared with hemoglobin  $\geq 14$  g/dL.<sup>36</sup> In the Dutch

aspirin score, anemia (defined by diagnosis-related groups) was also found to be one of the most important predictors of a first upper gastrointestinal bleed on aspirin therapy (adjusted HR, 2.3 [95% CI, 1.9–2.8];  $P<0.01$ ).<sup>37</sup> In PRECISE-DAPT, each 1-g/dL increase in hemoglobin between 10 and 12 g/dL was independently associated with a reduction in the risk of TIMI major/minor bleeding at 1 year (adjusted HR, 0.67 [95% CI, 0.53–0.84];  $P=0.001$ ).<sup>32</sup>

## Prior bleeding and transfusion

Spontaneous (nonintracranial) bleeding requiring hospitalization or transfusion in the past 6 months (or at any time if recurrent) is considered a major ARC-HBR criterion, and a first spontaneous (nonintracranial) bleed requiring hospitalization or transfusion >6 and <12 months before PCI is considered a minor ARC-HBR criterion (Table 3).

Information on the risk of subsequent bleeding in patients with a prior bleeding event who undergo PCI is scarce. Nonetheless, in the PRECISE-DAPT score, prior spontaneous bleeding at any time was found to be an important predictor of future bleeding and, in isolation, places patients in the highest quartile for bleeding risk.<sup>32</sup> In patients (n=320) presenting with peptic ulcer bleeding on aspirin monotherapy randomized to treatment with clopidogrel versus aspirin plus esomeprazole after confirmed ulcer healing, respective 1-year rates of recurrent ulcer bleeding (defined in the Appendix in the online-only Data Supplement) were 8.6% versus 0.7% (difference, 7.9% [95% CI, 3.4–12.4];  $P=0.001$ ).<sup>68</sup> In another randomized trial in patients (n=153) with acute peptic ulcer bleeding on aspirin monotherapy, recurrent ulcer bleeding (defined in the Appendix in the online-only Data Supplement) at 30 days occurred in 10.3% versus 5.4% of patients allocated to aspirin plus pantoprazole versus aspirin discontinuation (HR, 1.9 [95% CI, 0.6–6.0];  $P=0.25$ ).<sup>69</sup>

Data on the association between previous blood transfusion and subsequent bleeding risk in patients undergoing PCI are scarce. In 1 randomized trial of transfusion strategies in patients without PCI with acute upper gastrointestinal bleeding, patients (n=921) were assigned to a restrictive (maintain hemoglobin >7 g/dL) or liberal (maintain hemoglobin >9 g/dL) transfusion strategy. The rate of further in-hospital bleeding (defined in the Appendix in the online-only Data Supplement) was significantly lower in patients allocated to the restrictive strategy (10% versus 16%; adjusted HR, 0.68 [95% CI, 0.47–0.98];  $P=0.03$ ).<sup>70</sup> The highest rates of recurrent bleeding occurred in the setting of acute blood transfusion, suggesting that the timing of transfusion appears to be an important determinant of bleeding risk. Bleeding rates at 1 year were not reported.

## Thrombocytopenia

Moderate or severe baseline thrombocytopenia (platelet count <100  $\times 10^9$ /L) is considered a major ARC-HBR criterion (Table 3).

Baseline thrombocytopenia refers to thrombocytopenia that is present before PCI. This is distinct from acquired thrombocytopenia after PCI, which results from a postprocedural decline in platelet count in a patient without baseline thrombocytopenia. Thrombocytopenia is classified as mild (100–149  $\times 10^9$ /L), moderate (50–99  $\times 10^9$ /L), or severe (<50  $\times 10^9$ /L).<sup>71</sup> The reported prevalence of baseline thrombocytopenia in patients undergoing PCI is  $\approx 2.5\%$  in the United States and 1.5% in Japan.<sup>72,73</sup> Patients with

thrombocytopenia are underrepresented in randomized trials of DES and DAPT, and those who are enrolled generally have no more than mild thrombocytopenia because a platelet count of  $<100 \times 10^9/L$  is a common exclusion criterion.

Thrombocytopenia is a risk factor for both bleeding and ischemic complications. In an analysis from the US Nationwide Inpatient Sample (NIS) database, 32 565 patients with chronic thrombocytopenia at the time of PCI were propensity-matched with patients without thrombocytopenia.<sup>72</sup> The risks of in-hospital postprocedural bleeding, defined by *International Classification of Diseases* codes for in-hospital complications (10.9% versus 4.9%; odds ratio [OR], 2.40 [95% CI, 2.05–2.72];  $P < 0.0001$ ), and mortality (6.5% versus 2.9%; OR, 2.30 [95% CI, 1.90–2.70];  $P < 0.0001$ ) were significantly higher in patients with thrombocytopenia.<sup>72</sup> A post hoc analysis of patients with ST-segment-elevation myocardial infarction treated with PCI in the HORIZONS-AMI trial (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction;  $n=3476$ ) showed a higher rate of 30-day ACRITY (Acute Catheterization and Urgent Intervention Triage Strategy)-HORIZONS major bleeding (defined in the Appendix in the online-only [Data Supplement](#)) in 146 patients with baseline mild thrombocytopenia compared with those without thrombocytopenia (15.4% versus 9.1%;  $P=0.01$ ).<sup>74</sup>

Bleeding risk appears to be proportional to the degree of thrombocytopenia. A pooled analysis of 3 Japanese studies including patients undergoing PCI ( $n=19\,353$ ) showed increased rates of GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) moderate/severe bleeding (defined in the Appendix in the online-only [Data Supplement](#)) at 3 years in patients with baseline mild thrombocytopenia (9.9% versus 6.9%; adjusted HR, 1.20 [95% CI, 1.03–1.40];  $P=0.02$ ) and moderate/severe thrombocytopenia (23.1% versus 6.9%; adjusted HR, 2.35 [95% CI, 1.80–3.08];  $P < 0.001$ ) compared with patients without thrombocytopenia.<sup>73</sup>

## Chronic bleeding diatheses

The presence of a clinically significant chronic bleeding diathesis is considered a major ARC-HBR criterion ([Table 3](#)).

Chronic bleeding diatheses include inherited or acquired conditions known to be associated with increased bleeding risk such as platelet dysfunction, von Willebrand disease (prevalence of 1%–2% in the general population), inherited or acquired clotting factor deficiencies (including factors VII, VIII [hemophilia A], IX [hemophilia B], and XI), or acquired antibodies to clotting factors, among others.<sup>75–77</sup> For the purpose of the current HBR definition, thrombocytopenia is discussed separately.

Data on bleeding rates after PCI in patients with bleeding diatheses are scarce because such patients are generally excluded from DES and DAPT trials. In ZEUS-HBR, hematologic disorders or any known coagulopathy-associated bleeding diathesis (including prior or current thrombocytopenia, defined as platelet count  $<100 \times 10^9/L$ ) was a criterion conferring HBR status in 95 patients (11.5%).<sup>5</sup>

Among 796 patients with von Willebrand disease followed up for 1 year, 75 (9.4%) required clotting factor replacement therapy for 232 bleeding events.<sup>75</sup> In a series of 54 patients with hemophilia A or B undergoing coronary angiography or PCI, major periprocedural bleeding occurred in 3 patients (6%), and 11 patients (20%) had a bleeding event (predominantly minor) within 1 year.<sup>78</sup> The most

important and reliable predictor of bleeding in patients with bleeding diatheses is a personal history of bleeding, which may be assessed with a bleeding questionnaire.<sup>79</sup> However, given the lack of data and the low prevalence of such conditions in patients undergoing PCI, attempting to weight the differential bleeding risks with different bleeding diatheses and their levels of severity is beyond the scope of the current definition.

## Cirrhosis with portal hypertension

The presence of cirrhosis with portal hypertension is considered a major ARC-HBR criterion ([Table 3](#)).

The reported prevalence of cirrhosis in patients undergoing PCI in the United States is 1.2%.<sup>80</sup> The bleeding risk in chronic liver disease may be related to impaired hemostasis (resulting from coagulation factor deficiency, thrombocytopenia, platelet dysfunction, or increased fibrinolysis)<sup>81</sup> or to esophageal varices in the presence of portal hypertension. Bleeding complications on antithrombotic therapy in such patients are potentially catastrophic.<sup>82</sup>

Patients with severe liver disease are generally excluded from DES and DAPT trials. In the LEADERS FREE trial, although severe chronic liver disease was an inclusion criterion for HBR,  $<1\%$  of enrolled patients fulfilled this criterion.<sup>4</sup> The finding of obstructive CAD during transplantation workup in patients with end-stage liver disease is an increasingly common scenario. A single-center study of patients ( $n=1221$ ) who underwent orthotopic liver transplantation over a 10-year period in the United States reported that 38.6% of patients underwent coronary angiography and 4.7% underwent PCI before transplantation, with rates of both increasing over time.<sup>83</sup>

Data from the NIS registry ( $n=4\,376\,950$ ) showed that liver disease was an independent predictor of in-hospital gastrointestinal bleeding in patients undergoing PCI (OR, 2.59 [95% CI, 2.22–3.02];  $P < 0.001$ ).<sup>84</sup> In another retrospective study of PCI procedures ( $n=1\,051\,252$ ) in the NIS, 26.0% of patients with cirrhosis had a coagulopathy at baseline, 20.5% had anemia, and 3.9% had a hematologic or oncological malignancy.<sup>80</sup> The in-hospital mortality rate over the study period (3.6%) was higher compared with historical studies of the NIS database (0.5%–1.1%), and the most common postprocedural complications were hemorrhage (6.6% of patients) and the need for transfusion (11.3% of patients). In a retrospective study of patients with cirrhosis and CAD ( $n=148$ ) treated by either coronary stenting with DAPT or medical therapy with aspirin monotherapy, the rate of gastrointestinal bleeding at 1 year was 22% versus 5%, respectively ( $P=0.003$ ).<sup>85</sup> An observational study of patients with chronic hepatitis B virus ( $n=1674$ ) showed significantly higher bleeding rates (defined as International Society on Thrombosis and Haemostasis major bleeding or clinically relevant nonmajor bleeding)<sup>86,87</sup> in patients taking antiplatelet therapy compared with those without antiplatelet therapy (9.5% versus 1.8%; HR, 3.28 [95% CI, 1.98–5.42];  $P < 0.001$ ).<sup>88</sup> Although Child-Pugh and Mayo End-Stage Liver Disease criteria are used as exclusion criteria in some DES and DAPT trials, such scores were validated for predicting mortality in end-stage liver disease but not for predicting bleeding risk.<sup>89–91</sup>

## Cancer

Active malignancy (excluding nonmelanoma skin cancer) is considered a major ARC-HBR criterion ([Table 3](#)). Active malignancy is defined as diagnosis within the previous 12 months or ongoing active

cancer treatment (surgery, radiotherapy, chemotherapy, or immunotherapy). Cancer that is considered to be in complete remission or requires only maintenance therapy (eg, tamoxifen for breast cancer) is not considered active.

The prevalence of current or previous cancer in patients undergoing PCI in the US NIS database increased from 6.3% in 2004 to 9.5% in 2014.<sup>92</sup> Of 6 571 034 patients undergoing PCI, 1.8% had a current cancer diagnosis and 5.8% had previous cancer. Current cancer was associated with higher rates of in-hospital bleeding (defined by International Classification of Diseases, Ninth Revision, Clinical Modification codes, shown in the Appendix in the online-only [Data Supplement](#)) compared with previous cancer and no cancer history (9.7% versus 4.2% versus 3.1%; OR [current versus no cancer], 1.92 [95% CI, 1.82–2.04] and OR [historical versus no cancer], 1.08 [95% CI, 1.03–1.13]) and ranged between 4.9% and 21.2% according to the type, site, and spread of the malignancy.<sup>92</sup> Bleeding in cancer patients may be caused by local invasion, by a secondary systemic process, or by cancer treatment (Table VI in the online-only [Data Supplement](#)).

The LEADERS FREE trial included 239 patients (9.7%) with non-skin cancer diagnosed or treated within 3 years before the index PCI,<sup>4</sup> with 1-year BARC 3 to 5 bleeding in 9.6%. In an observational study of patients  $\geq 65$  years of age undergoing PCI ( $n=22\,798$ ), late bleeding (defined as hospitalization for bleeding  $\leq 1$  year after discharge) was reported in 5.0% of patients with a history of cancer, which was an independent predictor of late bleeding (HR, 1.80 [95% CI, 1.09–2.96];  $P=0.02$ ).<sup>93</sup>

In the TRILOGY ACS trial (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes;  $n=9240$ ), cancer incidence and outcomes were prospectively assessed among patients treated with DAPT (including clopidogrel or prasugrel) after ACS.<sup>94</sup> A new diagnosis of cancer was made in 170 patients (1.8%), of whom 53.5% permanently discontinued DAPT and 59% required surgery or chemotherapy. GUSTO severe/life-threatening, or moderate bleeding occurred substantially more frequently among those with cancer versus those without (11.2% versus 1.5%).

## Previous ischemic stroke or ICH

The presence of a brain arteriovenous malformation (bAVM), previous ICH at any time, and moderate or severe ischemic stroke (National Institutes of Health Stroke Scale score  $\geq 5$  on presentation) within 6 months before PCI are all considered major ARC-HBR criteria. Ischemic stroke at any time not meeting the major criterion is considered a minor ARC-HBR criterion (Table 3).

In the SCAAR Registry (Swedish Coronary Angiography and Angioplasty Registry), 5% to 6% of patients undergoing PCI reported a prior stroke.<sup>95</sup> In the NCDR (National Cardiovascular Data Registry) Cath-PCI,  $\approx 12\%$  of enrolled patients had a history of cerebrovascular disease (defined as prior stroke or carotid stenosis).<sup>96</sup> Pivotal DES trials, however, excluded patients with a prior stroke within 6 months of enrollment (Table I in the online-only [Data Supplement](#)). In trials of DES in patients perceived to be at increased bleeding risk, the prevalence of prior stroke was low, and bleeding rates for this subgroup were not reported. In LEADERS FREE, 1.6% of patients had ischemic stroke within the prior 12 months, and 1.3% had prior ICH.<sup>4</sup> In ZEUS-HBR, prior stroke or transient ischemic attack (TIA) was reported in 8% of patients.<sup>5</sup> In the SENIOR trial,  $\approx 8\%$

of the enrolled population had previous ischemic stroke; prior ICH was an exclusion criterion.<sup>6</sup>

Trials of DAPT after ACS have also excluded patients with prior ICH but not prior ischemic stroke/TIA.<sup>97–99</sup> In the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel)–TIMI 38 trial, patients with prior TIA or stroke ( $>3$  months before inclusion) who received aspirin and prasugrel had higher rates of ischemic and hemorrhagic stroke at 15 months compared with patients without prior TIA/stroke (any stroke occurred in 6.5% [2.3% ICH] and 0.9% [0.2% ICH], respectively), resulting in a contraindication for prasugrel use in such patients.<sup>99</sup> In contrast, in patients treated with aspirin and clopidogrel, rates of subsequent stroke did not significantly differ between patients with and those without prior TIA/stroke (1.2% [0% ICH] and 1.0% [0.3% ICH], respectively). In the PLATO trial (Platelet Inhibition and Patient Outcomes;  $n=18\,624$ ), patients with prior TIA/stroke ( $n=1152$ , 6.2%) treated with DAPT (including ticagrelor or clopidogrel) after PCI had significantly higher 1-year rates of ICH compared with those without prior stroke or TIA (0.8% versus 0.2%; unadjusted HR, 3.95 [95% CI, 1.82–8.55];  $P=0.0005$ ), with no significant difference in ICH rates between treatment groups (0.9% for ticagrelor versus 0.7% for clopidogrel; HR, 1.00 [95% CI, 0.25–3.99]).<sup>100</sup> In the TRA-2P [Trial to Assess the Effects of Vorapaxar (SCH 530348; MK-5348) in Preventing Heart Attack and Stroke in Patients With Atherosclerosis]–TIMI-50 trial ( $n=26\,449$ ), patients with prior stroke 2 weeks to 1 year before enrollment ( $n=5746$  [21.7%]) had a significantly higher rate of ICH at 3 years with vorapaxar compared with placebo added to standard antiplatelet therapy (2.4% versus 0.9%; HR, 2.55 [95% CI, 1.52–4.28];  $P<0.001$ ).<sup>101</sup> The rates of ICH in patients without prior stroke were markedly lower in both treatment groups (0.6% [vorapaxar arm] and 0.4% [placebo arm]; HR, 1.55 [95% CI, 1.00–2.41];  $P=0.049$ ).

Rates of non-ICH bleeding do not appear to differ significantly between patients undergoing PCI with and without previous stroke. In PRECISE-DAPT, patients with and without prior stroke had similar rates of TIMI major/minor bleeding (HR, 1.16 [95% CI, 0.54–2.48];  $P=0.70$ ).<sup>32</sup> In PARIS, rates of BARC 3 or 5 bleeding in patients with and without previous stroke were also similar (4.1% and 3.5%, respectively;  $P=0.66$ ).<sup>38</sup>

Six major randomized trials have investigated potent antiplatelet therapy for secondary stroke prevention (Table 5).<sup>102–107</sup> Three trials enrolled patients with acute minor stroke or TIA ( $<12$ –24 hours; National Institutes of Health Stroke Scale score  $<3$ –5) and showed no significant difference in ICH rates between patients treated with either DAPT or ticagrelor and those treated with aspirin monotherapy for 90 days.<sup>102–104</sup> MATCH (Management of Atherothrombosis With Clopidogrel in High-Risk Patients) and PROfESS (Prevention Regimen for Effectively Avoiding Second Strokes) enrolled patients with recent stroke ( $\leq 90$ –120 days). In both trials, overall rates of bleeding and primary ICH were higher with DAPT compared with clopidogrel monotherapy, without a significant reduction in ischemic events.<sup>105,106</sup> The SPS3 trial (Secondary Prevention of Small Subcortical Strokes) patients also showed significantly higher major bleeding rates and no significant reduction in recurrent stroke with DAPT compared with aspirin monotherapy in patients with recent symptomatic lacunar infarcts ( $\leq 180$  days).<sup>107</sup> However, in contrast to MATCH and PROfESS, rates of ICH were comparable between

**Table 5** Major Randomized Trials of Antiplatelet Therapy in Recent or Acute Ischemic Stroke or TIA

| Trial (Year of Publication)                            | Patients, n | Indication  | Experimental Arm   | Control Arm                   | Duration of Treatment and Follow-Up | Ischemic (Efficacy) Outcomes   | Bleeding (Safety) Outcomes   |
|--|-------------|---|--|-------------------------------|-------------------------------------|--|--|
| Trials of antiplatelet therapy in recent stroke or TIA |             |   |  |                               |                                     |  |  |
| MATCH (2004)105  | 7599        | Recent ischemic stroke or TIA (<3 mo) + ≥1 additional vascular risk factor (all patients were on clopidogrel monotherapy at baseline)                 | Aspirin 75 mg once daily plus clopidogrel 75 mg once daily                   | Clopidogrel 75 mg once daily  | 18 mo                               | Composite of ischemic stroke, MI, readmission, or vascular death: 15.7% vs 16.7% (absolute risk reduction, 1% [95% CI, -0.6 to 2.7]; P=0.244)*<br>Ischemic stroke: 8% vs 9% (absolute risk reduction, 0.62% [95% CI, -0.6 to 1.9]; P=0.353)              | Life-threatening bleeding: 2.6% vs 1.3% (absolute risk increase, 1.3% [95% CI, 0.6 to 1.9]; P<0.0001)<br>Primary ICH: 1% vs <1% (absolute risk increase, 0.40 [95% CI, 0.04 to 0.76]; P=0.029) |
| PRoFESS (2008)106                                      | 20 332      | Recent ischemic stroke (<90 d before randomization) + age ≥50 y or ischemic stroke 90–120 d before randomization + 2 additional vascular risk factors | Aspirin 25 mg plus extended-release dipyridamol 200 mg twice daily           | Clopidogrel 75 mg once daily† | 30 mo                               | Stroke (any): 9.0% vs 8.8% (HR, 1.01 [95% CI, 0.92 to 1.11])*<br>Ischemic stroke: 7.7% vs 7.9% (HR, 0.97 [95% CI, 0.88 to 1.07]; P=NS)<br>Composite of stroke, MI, or death from vascular causes: 13.1% in both groups (HR, 0.99 [95% CI, 0.92 to 1.07]) | Major bleeding: 4.1% vs 3.6% (HR, 1.15 [95% CI, 1.00 to 1.32])<br>ICH: 1.4% vs 1.0% (HR, 1.42 [95% CI, 1.11 to 1.83]; P=0.006)   |
| SPS3 (2012)107   | 3020        | Recent symptomatic lacunar infarct (≤180 d before randomization)  | Aspirin 325 mg once daily plus clopidogrel 75 mg once daily                  | Aspirin 325 mg once daily     | Mean, 3.4 y (range, 0–8.2 y)        | Stroke (any): 2.5%/y vs 2.7%/y (HR, 0.92 [95% CI, 0.72 to 1.16]; P=0.48)*<br>Ischemic stroke: 2.0%/y vs 2.4%/y (HR, 0.82 [95% CI, 0.63 to 1.09]; P=0.13)<br>Death: 2.1% vs 1.4% (HR, 1.52 [95% CI, 1.14 to 2.04]; P=0.004)                               | Major bleeding: 2.1%/y vs 1.1%/y (HR, 1.97 [95% CI, 1.41 to 2.71]; P<0.001)<br>ICH: 0.42%/y vs 0.28%/y (HR, 1.52 [95% CI, 0.79 to 2.93]; P=0.21)   |
| Trials of antiplatelet therapy in acute stroke or TIA  |             |   |  |                               |                                     |  |  |
| CHANGE (2014)102                                       | 5170        | Acute (≤24 h) minor ischemic stroke (NIHSS score ≤3) or high-risk TIA†  | Clopidogrel 75 mg once daily + aspirin 75 mg once daily (for the first 21 d) | Aspirin 75 mg once daily      | 90 d                                | Stroke (any): 8.2% vs 11.7% (HR, 0.68 [95% CI, 0.58 to 0.82]; P<0.001)*<br>Ischemic stroke: 7.9% vs  | Moderate or severe bleeding (GUSTO): 0.3% in both arms (P=0.73)<br>Hemorrhagic stroke: 0.3% in   |

Continued



**Table 5** Continued

| Trial (Year of Publication)    | Patients, n | Indication   | Experimental Arm   | Control Arm                  | Duration of Treatment and Follow-Up | Ischemic (Efficacy) Outcomes   | Bleeding (Safety) Outcomes  |
|--------------------------------|-------------|--|--|------------------------------|-------------------------------------|--|---|
| SOCRATES (2016) <sup>103</sup> | 13 199      | Acute ( $\leq 24$ h) nonsevere ischemic stroke (NIHSS score $\leq 5$ ) or high-risk TIA† or symptomatic intracranial or extracranial arterial stenosis | Ticagrelor 90 mg twice daily                                   | Aspirin 100 mg once daily    | 90 d                                | 11.4% (HR, 0.67 [95% CI, 0.56 to 0.81]; $P < 0.001$ )<br>Composite of stroke, MI, or cardiac death: 8.4% vs 11.9% (HR, 0.68 [95% CI, 0.59 to 0.82]; $P < 0.001$ )<br>Stroke, MI, or death: 6.8% vs 7.5% (HR, 0.89 [95% CI, 0.78 to 1.01]; $P = 0.07$ )*<br>Ischemic stroke: 5.9 vs 6.6% (HR, 0.87 [95% CI, 0.76 to 1.00]; $P = 0.05$ ) | both arms (HR, 1.01 [95% CI, 0.38 to 2.70]; $P = 0.98$ )  |
| POINT (2018) <sup>104</sup>    | 4881        | Acute ( $\leq 12$ h) minor ischemic stroke (NIHSS score $\leq 3$ ) or high-risk TIA†   | Aspirin 50–325 mg once daily plus clopidogrel 75 mg once daily | Aspirin 50–325 mg once daily | 90 d                                | Composite of ischemic stroke, MI, or death resulting from an ischemic vascular event: 5.0% vs 6.5% (HR, 0.75 [95% CI, 0.59 to 0.95]; $P = 0.02$ )*<br>Ischemic stroke: 4.6% vs 6.3% (HR, 0.72 [95% CI, 0.56–0.92]; $P = 0.01$ )  | Major bleeding: 0.9% vs 0.4% (HR, 2.32 [95% CI 1.10 to 4.87]; $P = 0.02$ )<br>Hemorrhagic stroke: 0.2% vs 0.1% (HR, 1.68 [95% CI, 0.40 to 7.03]; $P = 0.47$ ) |

Bleeding definitions are shown in the Appendix in the online-only [Data Supplement](#). CHANCE indicates Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HR, hazard ratio; ICH, intracranial hemorrhage; MATCH, Management of Atherothrombosis With Clopidogrel in High-Risk Patients; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; NS, not significant; PLATO, Study of Platelet Inhibition and Patient Outcomes; POINT, Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke; PROFESS, Prevention Regimen for Effectively Avoiding Second Strokes; SOCRATES, Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes; SP53, Secondary Prevention of Small Subcortical Strokes; and TIA, transient ischemic attack.

\*Primary outcome.

†High-risk TIA in CHANCE, SOCRATES, and POINT was defined as TIA with a moderate to high risk of stroke recurrence (defined as ABCD2 stroke risk score of  $\geq 4$ ; ABCD score assesses the risk of stroke based on age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes mellitus; scores range from 0–7, with higher scores indicating greater short-term risk of stroke).

‡Protocol amendment in PROFESS: because of a concern with an increased risk of bleeding, after 2027 patients had been enrolled, the clopidogrel plus aspirin arm was modified, and the next 18 305 patients were randomized to either clopidogrel alone or the unmodified combination of low-dose aspirin and dipyridamol.



treatment groups, but mortality rates were significantly higher with DAPT. In line with these findings, American Stroke Association/American Heart Association guidelines recommend (Class IIa, Level of Evidence B-R) that DAPT (aspirin and clopidogrel) initiated within 24 hours can be beneficial for early secondary prevention for a period of up to 90 days,<sup>108</sup> but it is not recommended (Class III, Level of Evidence A) for routine long-term secondary prevention after minor stroke or TIA.<sup>109</sup>

There is a lack of prospective data on DAPT and bleeding risk in patients with large strokes, prior ICH, and bAVMs. Patients with bAVMs have a high long-term risk of ICH.<sup>110</sup> In a patient-level meta-analysis of 2525 patients with bAVM, the annual risk of first and recurrent ICH was 1.3% (95% CI, 1.0–1.7) and 4.8% (95% CI, 3.9–5.9), respectively.<sup>111</sup> In a randomized study of unruptured bAVMs (n=223), the annual first ICH rate without interventional therapy was 2.0%.<sup>112</sup> The incremental risk of ICH in patients with bAVM taking antiplatelet therapy is not known.

## Planned major noncardiac surgery after PCI

Planned nondeferrable major surgery on DAPT after PCI is considered a major ARC-HBR criterion (Table 3).

After PCI, up to 17% of patients undergo an invasive diagnostic or therapeutic procedure within 1 year.<sup>113,114</sup> The increased risk of bleeding in a patient on antiplatelet therapy undergoing major surgery must be balanced against the potential risks of discontinuing DAPT in the potentially prothrombotic perioperative setting.<sup>113,114</sup> Important considerations include (1) the temporal relationship between PCI and surgery, (2) whether the surgery is deferrable, (3) the anticipated bleeding risk specific to the surgical procedure, and (4) the anticipated thrombotic risk as defined by patient, lesion, and procedural characteristics.

In the POISE-2 trial (Perioperative Ischemic Evaluation 2; n=10 010), 30-day major bleeding rates (defined in the Appendix in the online-only Data Supplement) after noncardiac surgery were higher with aspirin compared with placebo (4.6% versus 3.8%; HR, 1.23 [95% CI, 1.01–1.49];  $P=0.04$ ).<sup>115</sup> Although clinical practice guidelines provide recommendations on perioperative management of antithrombotic therapy, they do not define the perioperative bleeding risk of different surgical procedures.<sup>116,117</sup> To this end, a number of national multidisciplinary expert consensus documents have been published in an effort to standardize perioperative management of antithrombotic therapy based on balancing the predicted patient-specific ischemic risk with the anticipated procedure-specific bleeding risk.<sup>118–120</sup>

In summary, DAPT at the time of or shortly after surgery increases bleeding risk. Most elective surgery can be deferred beyond the proposed DAPT duration, and elective PCI is rarely necessary before elective major surgery. For urgent or nondeferrable surgery, the risk of stent thrombosis is much higher during the first month after PCI compared with subsequent months.<sup>121,122</sup>

## PCI after recent major surgery or trauma

Major surgery or major trauma 30 days before PCI is considered a major ARC-HBR criterion (Table 3).

The reported incidence of perioperative myocardial infarction after major noncardiac surgery is as high as 10%, depending on both

patient and procedural characteristics.<sup>123</sup> No data are available on bleeding rates when urgent PCI is required after recent major surgery or trauma. The bleeding risk of different types of surgery (including trauma surgery) has been reviewed recently.<sup>118</sup>

## Long-term oral NSAID or steroid use

Long-term steroid or oral NSAID use (defined as planned daily intake for  $\geq 4$  d/wk) is considered a minor ARC-HBR criterion (Table 3).

NSAIDs represent the most widely used class of medications worldwide.<sup>124,125</sup> Both oral NSAIDs and steroids are associated with increased gastrointestinal bleeding risk, which is dose-dependent and increases with long-term use.<sup>126,127</sup> There is a paucity of data on bleeding risk in patients with long-term oral NSAID or steroid use after PCI because of underrepresentation or underreporting in randomized trials. Although long-term NSAID or steroid use was an inclusion criterion in both LEADERS FREE and ZEUS-HBR, this criterion was met in only 72 patients (2.8%) and 25 patients (3%), respectively.<sup>4,5</sup> Moreover, their bleeding rates were not reported.

The risk of upper gastrointestinal bleeding is higher with NSAID monotherapy compared with aspirin monotherapy, and concomitant use of NSAIDs and aspirin substantially further increases the risk.<sup>37,128</sup> In the CONCERN trial (n=514), patients with arthritis presenting with upper gastrointestinal bleeding on NSAIDs with a requirement for low-dose aspirin were randomized to celecoxib or naproxen (plus aspirin and esomeprazole) after confirmed ulcer healing. Recurrent upper gastrointestinal bleeding (defined in the Appendix in the online-only Data Supplement) rates were 5.6% and 12.3% at 18 months, respectively (HR, 0.44 [95% CI, 0.23–0.82];  $P=0.008$ ).<sup>129</sup> In the CLASS study (Celecoxib Long-Term Arthritis Safety Study; n=8059), patients with arthritis were randomized to celecoxib or either ibuprofen or diclofenac. In the subgroup of patients taking aspirin, the rates of symptomatic upper gastrointestinal ulcers or complications (bleeding, perforation, and obstruction) at 6 months were 4.7% and 6.0%, respectively ( $P=0.49$ ).<sup>130</sup>

## Special considerations

### Frailty

Frailty was not included as a criterion because of the paucity of data demonstrating a causative role in bleeding in patients undergoing PCI and the lack of a consensus on how frailty is best assessed.<sup>131</sup> Bleeding risk may be increased in the setting of frailty as a result of more frequent falls, the inability to ambulate without assistance, or postural hypotension. When frailty was evaluated with a functional impairment score in the ACTION Registry (Acute Coronary Treatment and Intervention Outcomes Network), it was found to correlate with an increased risk of major in-hospital bleeding (defined in the Appendix in the online-only Data Supplement) in 112 000 elderly patients presenting with acute myocardial infarction undergoing cardiac catheterization. Major bleeding occurred in 6.4%, 10.3%, and 13.6% of patients with no, mild, and moderate to severe frailty, respectively (mild frailty–adjusted HR, 1.33 [95% CI, 1.23–1.44]; moderate to severe frailty–adjusted HR, 1.40 [95% CI, 1.24–1.58] compared with the group without frailty).<sup>132</sup> The inclusion of advanced age and coexisting ARC-HBR criteria may account, to

some degree, for frailty. Further studies on the impact of frailty on bleeding risk are encouraged.

## Ethnicity

The role of ethnicity in post-PCI bleeding risk has not been fully elucidated. Nonetheless, lower doses of several antithrombotic regimens are recommended in Asian patients compared with patients in Europe or the United States because of greater bleeding concerns in Asians.<sup>133,134</sup> Bleeding models developed in Western populations tend to underestimate bleeding risk in Asian populations.<sup>135</sup> In a patient-level meta-analysis, which pooled 7 randomized trials ( $n=16\,518$ ; 8605 East Asians, 7913 non-Asians), major bleeding occurred more frequently in East Asians (0.6% versus 0.3%;  $P=0.001$ ), whereas major adverse cardiac events occurred more frequently in non-East Asians (0.8% versus 1.8%;  $P<0.001$ ),<sup>136</sup> suggesting a differential ischemia/bleeding tradeoff in East Asians and non-East Asians. Further research is needed in this field.

## Acute Coronary Syndromes

Compared with stable patients with CAD, patients with ACS are at increased thrombotic risk, warranting treatment with more potent, longer-duration antiplatelet therapy. However, such an approach inevitably increases bleeding risk. In a meta-analysis of 3 randomized trials of patients with ACS ( $n=17\,393$ ) undergoing PCI with bivalirudin or heparin plus a glycoprotein IIb/IIIa inhibitor, the rate of TIMI major/minor bleeding was 5.3% at 30 days.<sup>137</sup> In selected patients with ST-segment-elevation myocardial infarction at low bleeding risk, respective 1-year rates of non-coronary artery bypass graft TIMI major/minor bleeding were 4.0% and 3.5% with ticagrelor and clopidogrel in the PLATO trial and 5.1% and 4.7% with prasugrel and clopidogrel in the TRITON-TIMI 38 trial.<sup>138,139</sup> Other trials of patients with ACS with more stringent exclusion criteria have reported 2-year BARC 3 to 5 bleeding rates as low as 0.5% to 0.8%.<sup>34</sup> Given that the increased bleeding risk in patients with ACS is attributable to the more aggressive antiplatelet therapy rather than the ACS per se, the consensus was not to consider ACS an HBR criterion.

## DAPT Nonadherence

DAPT nonadherence after PCI is well described. In the PARIS study, at a time when guidelines recommended  $\geq 12$  months of DAPT for all patients after stenting, the rate of DAPT discontinuation was 2.6%, 11.8%, and 19.9% at 30 days, 6 months, and 12 months, respectively.<sup>140</sup> In contrast, in trials investigating short DAPT regimens, nonadherence to recommended DAPT discontinuation may occur. For example, in the LEADERS FREE trial, despite a recommended 1-month DAPT duration,  $\approx 9\%$  remained on DAPT after 1 month.<sup>4</sup> In the SENIOR trial, 20% of patients remained on DAPT at 12 months, well beyond the recommended 1 to 6 months.<sup>6</sup> In the ZEUS trial, although all patients at HBR were prescribed DAPT for 30 days, 38% remained on DAPT at 2 months and 25% at 6 months.<sup>5,35</sup> Although DAPT nonadherence may increase the risk of thrombotic complications, nonadherence with recommended discontinuation may increase bleeding complications.

## Regulatory considerations

Studies of patients at HBR have intrinsic public health value and support the mission of regulatory bodies. Consensus definitions are necessary to improve the efficiency and predictability of study design and quality and can assist regulatory decision-making for safe and effective drugs and devices for patients at HBR in a timely fashion. Sex, nationality, and ethnic differences in bleeding risk may also be important considerations in trial design and the interpretation of study outcomes. This article reflects the consensus views of the ARC-HBR consortium and does not necessarily represent the practices, policies, requirements, or recommendations of the US Food and Drug Administration or the Japanese Pharmaceuticals and Medical Devices Agency. Furthermore, the recommendations in this document do not represent a regulatory requirement from either agency. Although regulators consider it acceptable to propose and justify alternative definitions and HBR criteria, they encourage investigators to discuss any proposed trial-specific definitions of HBR prospectively with the relevant regulatory bodies before study initiation.

## Limitations

A number of important limitations of the proposed definition must be acknowledged. First, the chosen cutoff values for 1-year BARC 3 or 5 bleeding (4%) and ICH (1%) are arbitrary, according to the expert opinion of this group. Second, data on rates of BARC 3 or 5 bleeding or ICH at 1 year were not available for a number of criteria, in which case justification is based on consensus decision alone. Third, although the relationship between many criteria and bleeding is continuous, binary criteria have been used to simplify the definition and to facilitate its use in trial enrollment. In addition, the differential bleeding risks associated with the criteria have not been weighted beyond major and minor because of a lack of data to support such an approach. Finally, the definition has not been validated in an independent patient data set. To this end, as more data become available, we anticipate validation and recalibration of this initial set of HBR criteria.

## Conclusions

In keeping with previous ARC initiatives, this ARC-HBR definition addresses an unmet need by providing a framework for evaluating treatment options for patients undergoing PCI at increased bleeding risk. It is expected that consistent use of the consensus definitions will improve our ability to tailor treatment to individual patient needs and to stimulate scientific progress, innovation, and quality control initiatives. We therefore encourage trialists and trial sponsors to consider using ARC-HBR definitions in clinical studies with reporting of BARC 3 or 5 bleeding rates to allow comprehensive and consistent assessment of patients at HBR.

The ARC-HBR group is cognizant that defining bleeding risk is the first step toward understanding the continuum of clinically meaningful risks and benefits in patients at HBR undergoing PCI. Evaluating and managing the risk of major bleeding must always be balanced by the

assessment of the thrombotic risk. This balance will be addressed in a future phase of the ARC-HBR initiative.

## Supplementary material

Supplementary material online is available at *European Heart Journal* online.

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